Dedi, S.
10/091007

30mar04 12:51:05 User219783 Session D2008.2

SYSTEM:OS - DIALOG OneSearch
File 65:Inside Conferences 1993-2004/Mar W4
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File 440:Current Contents Search(R) 1990-2004/Mar 30
(c) 2004 Inst for Sci Info
File 348:EUROPEAN PATENTS 1978-2004/Mar W03
(c) 2004 European Patent Office
File 357:Derwent Biotech Res. 1982-2004/Apr W1
(c) 2004 Thomson Derwent & ISI
File 113:European R&D Database 1997
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Set Items Description
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- Author(s)

Set Items Description
S1 345 AU=(LEPAGE, R? OR LEPAGE R? OR LE PAGE, R? OR LE PAGE R? OR LEPAGE, F? OR LEPAGE F? OR LE PAGE, F? OR LE PAGE F?)
S2 4878 AU=(WELLS M? OR WELLS, M? OR WELLS J? OR WELLS, J?)
S3 13 AU=(HANNIFY, B? OR HANNIFY B? OR HANNIFY S? OR HANNIFY, S? OR HANNIFFY, B? OR HANNIFFY B? OR HANNIFFY, S? OR HANNIFFY S?)
S4 8 S1 AND S2 AND S3
S5 48 S1 AND (S2 OR S3)
S6 10 S2 AND S3
S7 33 S5 AND (PROTEIN? ? OR POLYPROTEIN? ? OR POLYPEPTIDE? ? OR -PEPTIDE? ? OR AMINO)
S8 35 S4 OR S6 OR S7
S9 20 RD (unique items)
>>>No matching display code(s) found in file(s): 65, 113

9/3,AB/1 (Item 1 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)
(c) 2004 Inst for Sci Info. All rts. reserv.

17184338 Document Delivery Available: 000186063600007 References: 0
TITLE: Expression and delivery of heterologous antigens using lactic acid bacteria
AUTHOR(S): Reuter MA (REPRINT); **Hanniffy S; Wells JM;** Robinson A; Hudson MJ; Cranage MP
CORPORATE SOURCE: Food Res Inst, Norwich Res Pk/Norwich/Norfolk/England/ (REPRINT); Food Res Inst, /Norwich/Norfolk/England/
PUBLICATION TYPE: BOOK IN SERIES
PUBLICATION: VACCINE PROTOCOLS, SECOND EDITION, 2003, V87, P101-114
GENUINE ARTICLE#: BX66Z
BOOK SERIES TITLE: METHODS IN MOLECULAR MEDICINE
PUBLISHER: HUMANA PRESS INC, 999 RIVERVIEW DR, STE 208, TOTOWA, NJ 07512-1165 USA
ISBN: 1-58829-140-5 LIBRARY OF CONGRESS ID: 2003044968
LANGUAGE: English DOCUMENT TYPE: ARTICLE

9/3,AB/2 (Item 2 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)
(c) 2004 Inst for Sci Info. All rts. reserv.

Searcher : Shears 571-272-2528

10311960 References: 28
TITLE: 6-phosphogluconate dehydrogenase from Lactococcus lactis: a role for arginine residues in binding substrate and coenzyme
AUTHOR(S): Tetaud E; Hanau S; **Wells JM; Le Page RWF;** Adams MJ; Arkison S; Barrett MP (REPRINT)
AUTHOR(S) E-MAIL: m.barrett@bio.gla.ac.uk
CORPORATE SOURCE: Univ Glasgow, Div Infect & Immun, Joseph Black Bldg/Glasgow G12 8QQ/Lanark/Scotland/ (REPRINT); Univ Glasgow, Div Infect & Immun, /Glasgow G12 8QQ/Lanark/Scotland/; Univ Bordeaux 2, UPRESA 5016, /F-33076 Bordeaux//France/; Univ Ferrara, Dept Biochem & Mol Biol, /I-44000 Ferrara//Italy/; Univ Cambridge, Dept Pathol, /Cambridge CB2 1QP//England/; Univ Oxford, Dept Mol Biophys, /Oxford OX1 3QU//England/
PUBLICATION TYPE: JOURNAL
PUBLICATION: BIOCHEMICAL JOURNAL, 1999, V338, ,1 (FEB 15), P55-60
GENUINE ARTICLE#: 169QG
PUBLISHER: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON, ENGLAND W1N 3AJ
ISSN: 0264-6021
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: A gene encoding 6-phosphogluconate dehydrogenase (6-PGDH, EC 1.1.1.44) was identified from the homofermentative lactic acid bacterium Lactococcus lactis, by complementation of Escherichia coli mutants. The cloned gene was then expressed to high levels in E. coli and the **protein** purified for kinetic analysis. The enzyme had a K-m for 6-phosphogluconate of 15.4 +/- 1.4 mu M and for NADP of 1.9 +/- 0.2 mu M at pH 7.5. Sequence comparison of the L. lactis 6-PGDH with the corresponding enzyme derived from the pathogenic protozoan Trypanosoma brucei and sheep liver revealed the substrate-binding residues to be identical in all three species, although the three coenzyme-binding pockets differed slightly. A totally conserved arginine residue (Arg-447), believed to bind the 6-phosphate of substrate, was mutated to lysine, aspartate, alanine or tryptophan. In each case enzyme activity was lost, confirming an essential role for this residue on activity. A second arginine (Arg-34), believed to be critical in binding the 2'-phosphate of cofactor NADP(+), was mutated to a tyrosine residue, as found in one atypical isoform of the enzyme in Bacillus subtilis. This alteration led to decrease in affinity for NADP(+) of nearly three orders of magnitude. A second 6-PGDH gene has been identified from the genome of B. subtilis. This second isoform contains an arginine (Arg-34) in this position. suggesting that B. subtilis has two 6-PGDHs with different coenzyme specificities.

9/3,AB/3 (Item 3 from file: 440)

09594519 References: 49
TITLE: Mucosal delivery of murine interleukin-2 (IL-2) and IL-6 by recombinant strains of Lactococcus lactis coexpressing antigen and cytokine
AUTHOR(S): Steidler L; Robinson K; Chamberlain L; Schofield KM; Remaut E; **LePage RWF; Wells JM (REPRINT)**
CORPORATE SOURCE: UNIV CAMBRIDGE,DEPT PATHOL, CORTECS CTR VACCINE DISCOVERY, TENNIS COURT RD/CAMBRIDGE CB2 1QP//ENGLAND/ (REPRINT); UNIV CAMBRIDGE,DEPT PATHOL, CORTECS CTR VACCINE DISCOVERY/CAMBRIDGE CB2

Searcher : Shears 571-272-2528

1QP//ENGLAND/; STATE UNIV GHENT,/B-9000 GHENT//BELGIUM/; FLANDERS
INTERUNIV INST BIOTECHNOL,DEPT MOL BIOL/B-9000 GHENT//BELGIUM/
PUBLICATION TYPE: JOURNAL
PUBLICATION: INFECTION AND IMMUNITY, 1998, V66, N7 (JUL), P3183-3189
GENUINE ARTICLE#: ZW149
PUBLISHER: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW,
WASHINGTON, DC 20005-4171
ISSN: 0019-9567
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Lactococcus lactis is a nonpathogenic and noncolonizing bacterium which is being developed as a vaccine delivery vehicle for immunization by mucosal routes. To determine whether lactococci can also deliver cytokines to the immune system, we have constructed novel constitutive expression strains of L. lactis which accumulate a test antigen, tetanus toxin fragment C (TTFC), within the cytoplasmic compartment and also secrete either murine interleukin-2 (IL-2) or IL-6. When mice were immunized intranasally,vith various different expression strains of L. lactis, the anti-TTFC antibody titers increased more rapidly and were substantially higher in mice immunized with the bacterial strains which secreted IL-2 or IL-6 in addition to their production of TTFC. This adjuvant effect was lost when the recombinant strains of L. lactis were killed by pretreatment with mitomycin C and could therefore be attributed to the secretion of IL-2 or IL-6 by the recombinant lactococci. These results provide the first example of the use of a cytokine-secreting, noninvasive experimental bacterial vaccine vector to enhance immune responses to a coexpressed heterologous antigen and point the way to experiments which will test the possible therapeutic efficacy of this mode of cytokine delivery.

9/3,AB/4 (Item 4 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

08597394 References: 25
TITLE: Oral vaccination of mice against tetanus with recombinant Lactococcus lactis
AUTHOR(S): Robinson K; Chamberlain LM; Schofield KM; **Wells JM; LePage RWF (REPRINT)**
CORPORATE SOURCE: UNIV CAMBRIDGE,DEPT PATHOL, DIV MICROBIOL & PARASITOL, TENNIS COURT RD/CAMBRIDGE CB2 1QP//ENGLAND/ (REPRINT); UNIV CAMBRIDGE,DEPT PATHOL, DIV MICROBIOL & PARASITOL/CAMBRIDGE CB2 1QP//ENGLAND/
PUBLICATION TYPE: JOURNAL
PUBLICATION: NATURE BIOTECHNOLOGY, 1997, V15, N7 (JUL), P653-657
GENUINE ARTICLE#: XH583
PUBLISHER: NATURE PUBLISHING CO, 345 PARK AVE SOUTH, NEW YORK, NY 10010-1707
ISSN: 1087-0156
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: To determine whether a protective immune response could be elicited by oral delivery of a recombinant bacterial vaccine, tetanus toxin fragment C (TTFC) was expressed constitutively in Lactococcus lactis and administered orally to C57 BL/6 mice. The antibody titers elicited were lower than those following intranasal immunization (a route already known

to result in high-level systemic anti-TTFC immune responses) but the protective efficacy was the same order of magnitude. The serum antibody isotypes elicited were predominantly IgG1 and IgG2a. TTFC-specific fecal IgA responses could be detected following oral Or intranasal immunization. Chemically killed lactococci administered via the intranasal route were also able to elicit serum antibody responses of similar levels and kinetics to those induced by live bacteria.

9/3,AB/5 (Item 5 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

07719598 References: 53
TITLE: Lactic acid bacteria as vaccine delivery vehicles
AUTHOR(S): **Wells JM (REPRINT)** ; Robinson K; Chamberlain LM; Schofield KM; **LePage RWF**
CORPORATE SOURCE: UNIV CAMBRIDGE,DEPT PATHOL, TENNIS COURT RD/CAMBRIDGE CB2 1QP//ENGLAND/ (REPRINT)
PUBLICATION TYPE: JOURNAL
PUBLICATION: ANTONIE VAN LEEUWENHOEK INTERNATIONAL JOURNAL OF GENERAL AND MOLECULAR MICROBIOLOGY, 1996, V70, N2-4 (OCT), P317-330
GENUINE ARTICLE#: VG094
PUBLISHER: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS
ISSN: 0003-6072
LANGUAGE: English DOCUMENT TYPE: ARTICLE

9/3,AB/6 (Item 6 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

07513895 References: 27
TITLE: FACTORS AFFECTING THE IMMUNOGENICITY OF TETANUS TOXIN FRAGMENT C EXPRESSED IN LACTOCOCCUS LACTIS
AUTHOR(S): NORTON PM; BROWN HWG; **WELLS JM**; MACPHERSON AM; WILSON PW; **LEPAGE RWF**
CORPORATE SOURCE: AFRC,INST ANIM HLTH,COMPTON LAB/NEWBURY RG16 0NN/BERKS/ENGLAND/ (Reprint); UNIV CAMBRIDGE,DEPT PATHOL/CAMBRIDGE CB2 1QP//ENGLAND/
PUBLICATION: FEMS IMMUNOLOGY AND MEDICAL MICROBIOLOGY, 1996, V14, N2-3 (JUN), P167-177
GENUINE ARTICLE#: UU304
ISSN: 0928-8244
LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: The relative immunogenicity of tetanus toxin fragment C (TTF . C) has been determined in three different strains of inbred mice when expressed in Lactococcus lactis as a membrane-anchored **protein** (strain UCP1054), as an intracellular **protein** (strain UCP1050), or as a secreted **protein** which is partly retained within the cell wall (strain UCP1052). Protection against toxin challenge (20 x LD(50)) could be obtained without the induction of anti-lactococcal antibodies. When compared in terms of the dose of expressed tetanus toxin fragment C required to elicit protection against lethal challenge the

membrane-anchored form was significantly (10-20 fold) more immunogenic than the alternative forms of the **protein**.

9/3,AB/7 (Item 7 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

04985276 References: 13
TITLE: A MODEL SYSTEM FOR THE INVESTIGATION OF HETEROLOGOUS **PROTEIN** SECRETION PATHWAYS IN LACTOCOCCUS-LACTIS
AUTHOR(S): **WELLS JM**; WILSON PW; NORTON PM; **LEPAGE RWF**
CORPORATE SOURCE: UNIV CAMBRIDGE,DEPT PATHOL,DIV MICROBIOL & PARASITOL/CAMBRIDGE CB2 1QP//ENGLAND/ (Reprint)
PUBLICATION: APPLIED AND ENVIRONMENTAL MICROBIOLOGY, 1993, V59, N11 (NOV), P3954-3959
GENUINE ARTICLE#: ME660
ISSN: 0099-2240
LANGUAGE: ENGLISH DOCUMENT TYPE: NOTE

ABSTRACT: The capacity of recombinant strains of Lactococcus lactis to secrete a heterologous **protein** was investigated by constructing two expression-secretion vectors (pLET2 and pLET3) for use with a lactococcal gene expression system driven by the highly active T7 RNA polymerase. The vectors incorporated different lactococcal secretion leaders and translation initiation sequences. When tetanus toxin fragment C (TTFC) was used as a test **protein**, the quantities of TTFC produced by the pLET2-TTFC strain exceeded the rate of secretion of TTFC into the growth medium. However, nearly all of the soluble TTFC associated with the cell (3.4%) was translocated through the cell membrane. The pLET3-TTFC strain did not accumulate TTFC intracellularly and exhibited growth characteristics and viability identical to the growth characteristics and viability of the control strain. This strain secreted approximately 2.9 mg of TTFC per liter into the growth medium after 6 hof growth under test tube conditions. Our results indicate that L. lactis is capable of secreting substantial amounts of heterologous **protein** and also confirm the findings of other workers that the cell wall may serve as a functional barrier to the diffusion of some secreted **proteins** into the growth medium.

9/3,AB/8 (Item 8 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

04654049 References: 28
TITLE: LACTOCOCCUS-LACTIS - HIGH-LEVEL EXPRESSION OF TETANUS TOXIN FRAGMENT-C AND PROTECTION AGAINST LETHAL CHALLENGE
AUTHOR(S): **WELLS JM**; WILSON PW; NORTON PM; GASSON MJ; **LEPAGE RWF**
CORPORATE SOURCE: UNIV CAMBRIDGE,DEPT PATHOL,MUCOSAL IMMUNOL GRP/CAMBRIDGE CB2 1QP//ENGLAND/ (Reprint); AFRC,INST FOOD RES,DEPT GENET & MICROBIOL/NORWICH NR4 7UA/NORFOLK/ENGLAND/
PUBLICATION: MOLECULAR MICROBIOLOGY, 1993, V8, N6 (JUN), P1155-1162
GENUINE ARTICLE#: LJ085
ISSN: 0950-382X

LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: To determine if the food-grade bacterium Lactococcus lactis holds promise as a vaccine antigen delivery vector we have investigated whether this bacterium can be made to produce high levels of a heterologous **protein** antigen. A regulated expression system has been developed which may be generally suitable for the expression of foreign antigens (and other **proteins**) in L. lactis. The system utilizes the fast-acting T7 RNA polymerase to transcribe target genes, and provides the first example of the successful use of this polymerase in a Gram-positive bacterium. When the performance of the expression system was characterized using tetanus toxin fragment C (TTFC) up to 22% of soluble cell **protein** was routinely obtained as TTFC. Mice immunized subcutaneously with L. lactis expressing TTFC were protected from lethal challenge with tetanus toxin. These results show for the first time that L. lactis is able to express substantial quantities of a heterologous **protein** antigen and that this organism can present this antigen to the immune system in an immunogenic form.

9/3,AB/9 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01511325
SECRETED STREPTOCOCCUS PNEUMONIAE **PROTEINS**
SEKRETIERTE STREPTOCOCCUS PNEUMONIAE **PROTEINE**
PROTEINES
PATENT ASSIGNEE:
MICROBIAL TECHNICS LIMITED, (1944300), 20 Trumpington Street, Cambridge, CB2 1QA, (GB), (Applicant designated States: all)
Provalis UK Limited, (930085), Newtech Square, Deeside Industrial Park, Deeside, Flintshire CH5 2NT, (GB), (Applicant designated States: all)
INVENTOR:
LE PAGE, Richard, William, Falla, Gonville & Caius College, Cambridge CB2 1TA, (GB)
BADCOCK, Daniel, 3 Batten House, The Drive, Walthamstow, London E17 3BX, (GB)
SIZER, Philip, James, Holden, Provalis UK Limited, Newtech Square, Deeside Industrial Park, Deeside, Flintshire CH5 2NT, (GB)
PEEK, Keith, Provalis UK Limited, Newtech Square, Deeside Industrial Park , Deeside, Flintshire CH5 2NT, (GB)
WELLS, Jeremy, Mark, Institute of Food Research, Norwich Laboratory , Colney, Norwich NR4 7UA, (GB)
HANNIFFY, Sean, Bosco, Institute of Food Research, Norwich Laboratory, Colney, Norwich NR4 7UA, (GB
LEGAL REPRESENTATIVE:
Chapman, Paul William et al (73612), Kilburn & Strode, 20 Red Lion Street , London WC1R 4PJ, (GB)
PATENT (CC, No, Kind, Date): EP 1377605 A2 040107 (Basic)
WO 2002079241 021010
APPLICATION (CC, No, Date): EP 2002708512 020328; WO 2002GB1480 020328
PRIORITY (CC, No, Date): GB 108079 010330
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE; TR
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI

INTERNATIONAL PATENT CLASS: C07K-014/195
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English

9/3,AB/10 (Item 2 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01298331
NUCLEIC ACIDS AND **PROTEINS** FROM GROUP B STREPTOCOCCUS
NUKLEINSAUREN UND **PROTEINE** AUS GRUPPE-B STREPTOCOCCUS
ACIDES NUCLEIQUES ET PROTEINES PROVENANT DES STREPTOCOQUES DU GROUPE B
PATENT ASSIGNEE:
Microbial Technics Limited, (1944301), 38 Station Road, Cambridge CB1 2JH , (GB), (Applicant designated States: all)
INVENTOR:
LE PAGE, Richard W. F. University of Cambridge, Dept. of Pathology Tennis Court Road, Cambridge CB2 1QP, (GB)
WELLS, Jeremy Mark Institute of Food Research, Norwich Laboratory Norwich Research Park, Colney Norwich NR4 7UA, (GB)
HANNIFFY, Sean Bosco University of Cambridge, Dept. of Pathology Tennis Court Road, Cambridge CB2 1QP, (GB
LEGAL REPRESENTATIVE:
Chapman, Paul William et al (73612), Kilburn & Strode, 20 Red Lion Street , London WC1R 4PJ, (GB)
PATENT (CC, No, Kind, Date): EP 1214417 A2 020619 (Basic)
WO 200132882 010510
APPLICATION (CC, No, Date): EP 2000958822 000907; WO 2000GB3437 000907
PRIORITY (CC, No, Date): GB 9921125 990907
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12N-015/31; C12Q-001/68; C12N-001/21; C07K-014/315; C07K-016/12; A61K-039/09; A61K-048/00; G01N-033/53; G01N-033/68
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English

9/3,AB/11 (Item 3 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01135097
NUCLEIC ACIDS AND **PROTEINS** FROM STREPTOCOCCUS PNEUMONIAE
NUKLEINSAUREN UND ENTSPRECHENDE **PROTEINE** AUS STREPTOCOCCUS PNEUMONIAE
ACIDES NUCLEIQUES ET PROTEINES DE STREPTOCOCCUS PNEUMONIAE
PATENT ASSIGNEE:
MICROBIAL TECHNICS LIMITED, (1944300), 20 Trumpington Street, Cambridge, CB2 1QA, (GB), (Applicant designated States: all)
INVENTOR:
LE PAGE, Richard, William, Falla, University of Cambridge, Tennis Court Road, Cambridge CB2 1QP, (GB)

Searcher : Shears 571-272-2528

WELLS, Jeremy, Mark, Actinova Ltd., 12 Pembroke Avenue, Waterbeech, Cambridge CB5 9PB, (GB)
HANNIFFY, Sean, Bosco, University of Cambridge, Tennis Court Road, Cambridge CB2 1QP, (GB)
HANSBRO, Philip, Michael, CBVT Dis. Immun.Microbio, D. Maddison C. Scie. Building Royal Newcastle Hosp, Newcastle NSW 2300, (AU
LEGAL REPRESENTATIVE:
Chapman, Paul William et al (73612), Kilburn & Strode, 20 Red Lion Street , London WC1R 4PJ, (GB)
PATENT (CC, No, Kind, Date): EP 1144640 A2 011017 (Basic)
EP 1144640 A3 011128
WO 200006738 000210
APPLICATION (CC, No, Date): EP 99934990 990727; WO 99GB2452 990727
PRIORITY (CC, No, Date): GB 9816336 980727; US 125329 P 990319
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C12N-015/31; C07K-014/315; C07K-016/12; A61K-031/70; A61K-039/09; G01N-033/53; G01N-033/68; C12Q-001/68
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English

9/3,AB/12 (Item 4 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01135095
NUCLEIC ACIDS AND **PROTEINS** FROM GROUP B STREPTOCOCCUS
NUKLEINSAUREN UND ENTSPRECHENDE **PROTEINE** AUS GRUPPE-B STREPTOCOCCUS
ACIDES NUCLEIQUES ET PROTEINES DE STREPTOCOCCUS GROUPE B
PATENT ASSIGNEE:
MICROBIAL TECHNICS LIMITED, (1944300), 20 Trumpington Street, Cambridge, CB2 1QA, (GB), (Applicant designated States: all)
INVENTOR:
LE PAGE, Richard, William, Falla, U. of Cambridge D. of Pathology Tennis Court Road, Cambridge CB2 1QP, (GB)
WELLS, Jeremy, Mark Institute of Food Research, Norwich Laboratory Norwich Research Park, Colney Norwich NR4 7UA, (GB)
HANNIFFY, Sean, Bosco University of Cambridge, Dept. of Pathology Tennis Court Road, Cambridge CB2 1QP, (GB
LEGAL REPRESENTATIVE:
Chapman, Paul William et al (73612), Kilburn & Strode, 20 Red Lion Street , London WC1R 4PJ, (GB)
PATENT (CC, No, Kind, Date): EP 1100920 A2 010523 (Basic)
WO 200006736 000210
APPLICATION (CC, No, Date): EP 99934984 990727; WO 99GB2444 990727
PRIORITY (CC, No, Date): GB 9816335 980727; US 125163 P 990319
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12N-015/31; C12N-015/74; C12N-015/62; C12N-015/10; C12N-009/16; C12N-001/19; C12N-001/21; C07K-014/315; C07K-016/12; A61K-031/70; A61K-039/09; G01N-033/53; G01N-033/68; C12Q-001/68
NOTE:

No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English

9/3,AB/13 (Item 5 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00856009
DELIVERY OF BIOLOGICALLY ACTIVE **POLYPEPTIDES**
VERABREICHUNG VON BIOLOGISCH AKTIVEN **POLYPEPTIDEN**
ADMINISTRATION DE **POLYPEPTIDES** BIOLOGIQUEMENT ACTIFS
PATENT ASSIGNEE:
CAMBRIDGE UNIVERSITY TECHNICAL SERVICES LIMITED, (1046612), The Old Schools, Trinity Lane, Cambridge CB2 1TS, (GB), (applicant designated states: AT;BE;CH;DE;DK;ES;FI;FR;GB;GR;IE;IT;LI;LU;MC;NL;PT;SE)
INVENTOR:
STEIDLER, Lothar, Universiteit Gent, Lab. of Molecular Biology, K.L. Ledeganckstraat 35, B-9000 Gent, (BE)
REMAUT, Erik, Universiteit Gent, Lab. of Molecular Biology, K.L. Ledeganckstraat 35, B-9000 Gent, (BE)
WELLS, Jeremy Mark, University of Cambridge, Dept. of Pathology, Tennis Court Road, Cambridge CB2 1QP, (GB)
LE PAGE, Richard William Falla, Univ. of Cambridge, Dept. of Pathology, Tennis Court Road, Cambridge CB2 1QP, (GB
LEGAL REPRESENTATIVE:
Brants, Johan Philippe Emile et al (92671), De Clercq, Brants & Partner cv Edgard Gevaertdreef 10a, 9830 Sint-Martens-Latem, (BE)
PATENT (CC, No, Kind, Date): EP 871748 A2 981021 (Basic)
WO 9714806 970424
APPLICATION (CC, No, Date): EP 96935054 961021; WO 96GB2580 961021
PRIORITY (CC, No, Date): GB 9521568 951020
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C12N-015/74; A61K-039/02; A61K-039/085; A61K-039/09; C12N-015/12; C12N-015/16; C12N-015/19; C12N-015/24; C12N-015/26; C12N-015/31; C12N-001/21;
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English

9/3,AB/14 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0306341 DBR Accession No.: 2003-08126 PATENT
New Streptococcus pneumoniae **protein** or **polypeptide**, useful as an immunogen and/or antigen for use in vaccines against Streptococcus pneumoniae infection, and in diagnostic assays - vector-mediated recombinant **protein** gene transfer and expression in host cell and hybridoma cell culture for monoclonal antibody production for disease diagnosis, recombinant vaccine and gene therapy
AUTHOR: **LE PAGE R W F**; BADCOCK D; SIZER P J H; PEEK K; **WELLS J M**; **HANNIFFY S B**
PATENT ASSIGNEE: MICROBIAL TECHNICS LTD; PROVALIS UK LTD 2002

Searcher : Shears 571-272-2528

PATENT NUMBER: WO 200279241 PATENT DATE: 20021010 WPI ACCESSION NO.: 2003-103261 (200309)
PRIORITY APPLIC. NO.: GB 20018079 APPLIC. DATE: 20010330
NATIONAL APPLIC. NO.: WO 2002GB1480 APPLIC. DATE: 20020328
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A Streptococcus pneumoniae **protein** or **polypeptide** (I) comprising any of the 8 fully defined sequences of 28-567 **amino** acids given in the specification, or its homologue, derivative, or antigenic or immunogenic fragment, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) A nucleic acid molecule comprising: (a) any of the DNA sequences given in the specification, or their RNA equivalents; (b) a sequence which is complementary to (a); (c) a sequence which codes for (I) or its homologue, derivative or fragment; and/or (d) a sequence which is substantially identical to (a), (b) or (c); (2) An immunogenic and/or antigenic composition, comprising one or more (I) or its homologue, derivative or fragment; (3) A vaccine comprising (I) or the nucleic acid molecule, and one or more additional components such as an excipient, diluent, adjuvant or the like; (4) An antibody capable of binding to (I) or its homologue, derivative or fragment; (5) Detection or diagnosis of S. pneumoniae, comprising bringing into contact a sample to be tested with at least one **protein** or **polypeptide** cited above, or its homologue, derivative or fragment; the above antibody or the nucleic acid sequence; and (6) Determining whether (I) represents a potential anti-microbial target, comprising inactivating the **protein** or **polypeptide** and determining whether S. pneumoniae is still viable. WIDER DISCLOSURE - Also disclosed as new are: (a) Vaccinating a subject against S. pneumoniae infection; (b) Prophylaxis or treatment of S. pneumoniae infection; and (c) Kits for detecting or diagnosing S. pneumoniae infection. BIOTECHNOLOGY - Preferred **Protein/Polypeptide**: The **protein** or **polypeptide** is provided in substantially pure form, and has the N-terminal sequence Met Glu Leu Val Leu Pro Asn Asn Tyr Val Val (Asp,Ala) Ile (Leu) Asp (Glu) Glu (Gln) Glu Glu Met Met Tyr Leu Asp Gly Gly (Glu), where the bracketed residues represent alternatives to the preceding **amino** acid, its fragment, homologue or derivative. Preferred Antibody: The antibody is a monoclonal antibody. Preparation: The **protein/polypeptide**, nucleic acid and vaccine are produced by standard recombinant techniques. The antibody can be produced by hybridoma techniques. ACTIVITY - Antibacterial; Immunostimulant. No biological data given. MECHANISM OF ACTION - Vaccine; Gene therapy. No biological data given. USE - The **protein** or **polypeptide** , or its homologue, derivative or fragment, is useful as an immunogen and/or antigen that may be used in vaccines or diagnostic assays. The methods are useful for the selection/diagnosis of S. pneumoniae , and determining whether a **protein** or **polypeptide** represents a potential anti-microbial target. An agent capable of antagonizing, inhibiting or otherwise interfering with the function or expression of a **protein** or **polypeptide** is useful in the manufacture of a medicament for use in the treatment or prophylaxis of S.pneumoniae infection (all claimed). The agent capable of antagonizing, inhibiting or interfering with the function or expression of the **protein** or **polypeptide**, is useful in the manufacture of a medicament for the treatment or prophylaxis of S. pneumoniae infection (claimed).EXAMPLE - No relevant examples given. (43 pages)

Searcher : Shears 571-272-2528

9/3,AB/15 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0271324 DBR Accession Number: 2001-10548 PATENT
New **polypeptides** derived from Streptococcus agalactiae are useful to provide detection of, and vaccination against, Group-B Streptococcus infections, particularly to prevent infection in neonatals - recombinant **protein** production via plasmid expression in host cell useful for Streptococcus infection and for recombinant vaccine
AUTHOR: **Le Page R W F; Wells J M; Hanniffy S B**
CORPORATE SOURCE: Cambridge, UK.
PATENT ASSIGNEE: Microbial-Technics 2001
PATENT NUMBER: WO 200132882 PATENT DATE: 20010510 WPI ACCESSION NO.: 2001-316444 (2033)
PRIORITY APPLIC. NO.: GB 9921125 APPLIC. DATE: 19990907
NATIONAL APPLIC. NO.: WO 2000GB3437 APPLIC. DATE: 20000907
LANGUAGE: English
ABSTRACT: A group-B Streptococcus **protein** (P1) is claimed. (P1) contains one of the sequences fully defined, or its fragment or derivative. Also claimed are: derivatives or variants having at least 50% identity to P1; a nucleic acid (N1); a vector containing N1; transforming or transfecting a host with the vector; producing a P1; an antibody or affibody or its derivative which binds to P1; an immunogenic composition containing N1 or P1; detecting if a P1 represents a potential anti-microbial target; detecting Group-B Streptococcus by bringing into contact a sample to be tested with (N1); and determining if a **protein, polypeptide, peptide,** fragments or derivative of them represents a potential anti-microbial target. The invention is used to vaccinate against Group-B Streptococcus infection, particularly to prevent infection in new born children arising from the maternal genital tract. An immunogenic composition is useful in the preparation of a medicament for the treatment or prophylaxis of Group-B Streptococcus infection. (89pp)

9/3,AB/16 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0251450 DBR Accession Number: 2000-05940 PATENT
Streptococcal **proteins** and polynucleotides useful for diagnosis, treatment and prophylaxis of bacterial infections - recombinant vaccine, monoclonal antibody and nucleic acid vaccine
AUTHOR: **le Page R W F; Wells J M; Hanniffy S B;** Hansbro P M
CORPORATE SOURCE: Cambridge, UK.
PATENT ASSIGNEE: Microbial-Technics 2000
PATENT NUMBER: WO 200006738 PATENT DATE: 20000210 WPI ACCESSION NO.: 2000-195301 (2017)
PRIORITY APPLIC. NO.: US 125329 APPLIC. DATE: 19990319
NATIONAL APPLIC. NO.: WO 99GB2452 APPLIC. DATE: 19990727
LANGUAGE: English
ABSTRACT: Streptococcus pneumoniae **protein** (I) or **polypeptide,**

its homolog or derivative, having one of 12 fully disclosed **protein** sequences, is claimed. Also claimed are: a **protein** of **polypeptide** (II), its homolog or derivative, having a defined **protein** sequence selected from one of the 61 sequences disclosed; an antigenic and/or immunogenic fragment of (I), (II) or a **protein** or **polypeptide** (III) having a sequence selected form 12 defined sequence; a nucleic acid molecule encoding (I), (II) or (III) and having one of the disclosed DNA sequences (or being an RNA equivalent, complement, homolog, derivative or identical sequence); an immunogenic and/or antigenic composition of (I), (II), (III) or homologs, derivatives and/or fragments; a vaccine comprising (III); an antibody capable of binding to (I), (II), (III) or a homolog, derivative or fragment; and determining the anti-microbial activity of (I), (II) and (III) by inactivating the **protein** and determining the viability of S. pneumoniae. The DNA sequence can be used as a nucleic acid vaccine or in diagnosis. The antibody is preferably a monoclonal antibody produced by hybridoma cell culture. (76pp)

9/3,AB/17 (Item 4 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0251448 DBR Accession Number: 2000-05938 PATENT
New group B Streptococcus **protein**, useful as vaccine for diagnosis of Streptococcal infections and for screening of antibodies or affibodies - recombinant vaccine and nucleic acid vaccine
AUTHOR: **le Page R W F; Wells J M; Hanniffy S B**
CORPORATE SOURCE: Cambridge, UK.
PATENT ASSIGNEE: Microbial-Technics 2000
PATENT NUMBER: WO 200006736 PATENT DATE: 20000210 WPI ACCESSION NO.: 2000-195299 (2017)
PRIORITY APPLIC. NO.: US 125163 APPLIC. DATE: 19990319
NATIONAL APPLIC. NO.: WO 99GB2444 APPLIC. DATE: 19990727
LANGUAGE: English
ABSTRACT: A group B Streptococcus (GBS) (Staphylococcus aureus, Streptococcus sp. or Streptococcus pneumoniae) **protein** or **polypeptide** or **peptide** (I) having one of 69 disclosed **protein** sequences or 11 oligonucleotide DNA primers (III) of defined DNA sequence and their fragments or derivatives is claimed. Also claimed are: derivatives or variants of (I) having at least 50% homology to (I); a nucleic acid molecule having one of the disclosed DNA sequences or their RNA equivalents; a sequence complementary to the disclosed DNA sequences; a sequence encoding (I); a sequence with identity to the claimed sequences; a sequence which encodes a derivative or fragment of the disclosed nucleic acid molecules; a vector comprising DNA for expression of (I) or variants of (I); a host cell suitable for transformation; an antibody, an affibody or their derivative which binds to one or more of (I) or its variants; a kit for detecting GBS comprising at least one (I), (I) variant or an antibody or affibody derivative; screening for DNA encoding a bacterial cell envelope associated or surface antigens in Gram-pos. bacteria; and determining if (I) or its variant is a drug target. (123pp)

9/3,AB/18 (Item 5 from file: 357)

DIALOG(R)File 357:Derwent Biotech Res.

0227970 DBR Accession Number: 98-09567 PATENT
New non-invasive or non-pathogenic Gram-positive bacteria - containing DNA which encodes enzymes for production of a polysaccharide immunogen of a pathogenic bacteria, used as a recombinant vaccine
AUTHOR: **Wells J M; le Page R W F;** Gilbert C F G
CORPORATE SOURCE: Cambridge, UK.
PATENT ASSIGNEE: Microbial-Technics 1998
PATENT NUMBER: WO 9831786 PATENT DATE: 980723 WPI ACCESSION NO.: 98-414088 (9835)
PRIORITY APPLIC. NO.: GB 97939 APPLIC. DATE: 970117
NATIONAL APPLIC. NO.: WO 98GB156 APPLIC. DATE: 980119
LANGUAGE: English
ABSTRACT: Claimed is (A) a non-invasive/non-pathogenic Gram-pos. bacterium which is transformed with DNA coding for one or more enzymes responsible for the production of a polysaccharide immunogen (PSI) from a pathogenic bacterium. Also claimed are: (B) a method for the production of a pathogenic bacterium PSI which comprises transforming a non-invasive or non-pathogenic Gram-pos. bacterium with DNA which codes for one or more enzymes responsible for the production of the PSI and/or culturing the bacterium; (C) a DNA construct comprising DNA encoding one or more enzymes responsible for the production of a PSI from a pathogenic bacterium; (D) a vector comprising a DNA construct as in (C). The products can be used in vaccines against polysaccharide encapsulated pathogenic bacteria, e.g. Streptococcus pneumoniae, etc.. Suitable Gram-pos. bacteria include Listeria innocua, Staphylococcus xylosus, Staphylococcus carnosus, Streptococcus gordonii, Lactococcus sp. or Lactobacillus sp.. Alternatively, attenuated strains of a Gram-pos. pathogenic bacterium, e.g. vaccine strains of Listeria, e.g. Listeria monocytogenes can be used. (39pp)

9/3,AB/19 (Item 6 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0211807 DBR Accession Number: 97-06928 PATENT
Delivering active **peptides** and antigens in non-pathogenic bacteria - recombinant vaccine construction by antigen or recombinant **protein** expression in Listeria monocytogenes or Lactococcus lactis
AUTHOR: Steidler L; Remaut E; **Wells J M; Le Page R W F**
CORPORATE SOURCE: Cambridge, UK.
PATENT ASSIGNEE: Univ.Cambridge-Tech.Serv. 1997
PATENT NUMBER: WO 9714806 PATENT DATE: 970424 WPI ACCESSION NO.: 97-245121 (9722)
PRIORITY APPLIC. NO.: GB 9521568 APPLIC. DATE: 951020
NATIONAL APPLIC. NO.: WO 96GB2580 APPLIC. DATE: 961021
LANGUAGE: English
ABSTRACT: A method for delivering **proteins** and/or antigens (I) to a subject involves using a non-invasive or non-pathogenic Listeria innocua, Staphylococcus xylosus, Staphylococcus carnosus, Streptococcus gordoni, Lactococcus sp., Lactobacillus sp., especially Lactococcus lactis or Listeria monocytogenes expressing (I). (I) may be from a

eukaryote, prokaryote or a virus. (I) may be a cytokine, insulin, somatotropin, prolactin, calcitonin, leutinizing hormone, parathormone, somatostatin, thyrotropin or vasoactive intestinal **polypeptide** or a receptor or antagonist to (I). Also new are: methods for regulating survival, growth, differentiation, effector functions or infection susceptibility of cells or tissues, boosting an immune response, modulating an immune response, modulating infiltration of tissues with inflammatory/tumor cells, controlling tumor cell growth rate, inducing apoptosis in tumor cells, downregulating an immune response or treating an allergic autoimmune disease; a composition of the bacterium; a recombinant vaccine; DNA encoding (I); an artificial gene; and production of the transformant. (49pp)

9/3,AB/20 (Item 7 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0197925 DBR Accession Number: 96-08696
Progress in the development of Lactococcus lactis as a recombinant mucosal vaccine delivery system - recombinant vaccine construction using low copy number plasmid pILPoI encoding phage T7 RNA-polymerase
AUTHOR: Norton P M; **Le Page R W F; Wells J M**
CORPORATE AFFILIATE: Univ.Cambridge
CORPORATE SOURCE: Department of Pathology, University of Cambridge, Cambridge, UK.
JOURNAL: Folia Microbiol. (40, 3, 225-30) 1995
ISSN: 0015-5632 CODEN: FOMIAZ
LANGUAGE: English
ABSTRACT: A highly active over-expression system was developed for use in Lactococcus lactis, a potential antigen delivery agent for mucosal vaccination. The phage T7 RNA-polymerase (EC-2.7.7.6) gene was cloned under the control of the lactococcal promoter in low-copy number plasmid pIL227, derived from the enterococcal plasmid pAMb-1 replicon to generate plasmid pILPoI. When lactose was substituted for glucose in the culture medium, a metabolite of lactose - tagatose-6-phosphate - prevented the LacR repressor from binding to the operator site in the lac promoter, leading to the expression of phage T7 RNA-polymerase. Once formed in the cell, the phage T7 RNA-polymerase then transcribed genes cloned into the compatible plasmid pLET series of expression vectors. Tetanus toxin fragment C (TTFC) was used as a convenient initial experimental antigen as it was a potent immunogen. When the L. lactis expression strain carrying plasmid pLET1-TTFC was induced with lactose to express TTFC, this antigen accumulated intracellularly in amount up to 22% of the total soluble **protein**. (10 ref)
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Devi, S.
10/091007

(FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, PHIC, PHIN, TOXCENTER, PASCAL, DISSABS, FEDRIP' ENTERED AT 12:27:27 ON 30 MAR 2004)

L46	940	SEA ABB=ON PLU=ON ("LEPAGE F"? OR "LE PAGE F"? OR "LEPAGE R"? OR "LE PAGE R"?)/AU
L47	13758	SEA ABB=ON PLU=ON ("WELLS M"? OR "WELLS J"?)/AU
L48	18	SEA ABB=ON PLU=ON ("HANNIFY B"? OR "HANNIFFY B"? OR "HANNIFY S"? OR "HANNIFFY S"?)/AU
L49	8	SEA ABB=ON PLU=ON L46 AND L47 AND L48
L50	122	SEA ABB=ON PLU=ON L46 AND (L47 OR L48)
L51	12	SEA ABB=ON PLU=ON L47 AND L48
L52	48	SEA ABB=ON PLU=ON L50 AND (PROTEIN OR AMINO OR POLYPROTEIN OR PEPTIDE OR POLYPEPTIDE)
L53	52	SEA ABB=ON PLU=ON L49 OR L51 OR L52
L54	22	DUP REM L53 (30 DUPLICATES REMOVED)

Author(s)

L54 ANSWER 1 OF 22 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2003:433916 BIOSIS
DOCUMENT NUMBER: PREV200300433916
TITLE: Delivery of biologically active **polypeptides**
.
AUTHOR(S): Steidler, Lothar [Inventor, Reprint Author]; Remaut, Erik [Inventor]; **Wells, Jeremy Mark** [Inventor]; **Le Page, Richard William Falla** [Inventor]
CORPORATE SOURCE: Ghent, Belgium
ASSIGNEE: Vlaams Interuniversitair Instituut voor Biotechnologie, Zwijnaarde, Belgium; Microbial Technics Limited, Cambridge, UK
PATENT INFORMATION: US 6605286 August 12, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Aug 12 2003) Vol. 1273, No. 2. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Sep 2003
Last Updated on STN: 17 Sep 2003

AB Biologically active **polypeptides** and/or antigens are delivered by administering to a subject a non-invasive or non-pathogenic bacterium which expresses one or more antigens or **polypeptides**. The non-invasive or non-pathogenic bacterium can be included in delivery systems or pharmaceutical formulations.

L54 ANSWER 2 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2003:793313 HCAPLUS
DOCUMENT NUMBER: 139:375857
TITLE: Expression and delivery of heterologous antigens using lactic acid bacteria
AUTHOR(S): Reuter, Mark A.; **Hanniffy, Sean**; **Wells, Jerry M.**
CORPORATE SOURCE: Institute of Food Research, Colney, Norwich, UK
SOURCE: Methods in Molecular Medicine (2003), 87(Vaccine Protocols (2nd Edition)), 101-114

Searcher : Shears 571-272-2528

CODEN: MMMEFN
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB There has been increasing interest in developing delivery vehicles for use as mucosally administered vaccines. Lactobacillus lactis is a harmless noninvasive bacterium with a history of safe use in the food industry, which makes it more acceptable than attenuated pathogens for vaccine delivery. A number of potential vaccine antigens have now been expressed in L. lactis, but most immunol. studies have been carried out with L. lactis-producing tetanus toxin fragment C. Mucosally administered L. lactis expressing heterologous protein is capable of eliciting both local and systemic immune responses. The pTREX series of theta-replicating plasmid vectors, derived using the non-self-transmissible plasmid pIL253 that carries the broad Gram-pos. host replicon pAMβ1, has been used for both constitutive and inducible expression of heterologous protein antigens in L. lactis. Methods used when working with L. lactis are described with a view to using this bacterium to express and deliver heterologous proteins that can ultimately be developed to treat or prevent diseases in humans.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L54 ANSWER 3 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2002:777971 HCAPLUS
DOCUMENT NUMBER: 137:305769
TITLE: DNA and **protein** sequences of Streptococcus pneumoniae secretory **proteins** and the uses of **proteins** for development of vaccines
INVENTOR(S): **Le Page, Richard William Falla;** Badcock, Daniel; Sizer, Philip James Holden; Peek, Keith; **Wells, Jeremy Mark; Hanniffy, Sean Bosco**
PATENT ASSIGNEE(S): Microbial Technics Limited, UK; Provalis Uk Limited
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002079241	A2	20021010	WO 2002-GB1480	20020328
WO 2002079241	A3	20030814		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1377605 A2 20040107 EP 2002-708512 20020328

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: GB 2001-8079 A 20010330
WO 2002-GB1480 W 20020328

AB This invention provides DNA and **protein** sequences of secretory **proteins** cloned from Streptococcus pneumoniae. The invention also provides the expression pattern of the gene encoding one of the secretory **proteins**, LID-304 in different isolates of Streptococcus pneumoniae. The **proteins** can be used for development of vaccines for treatment of pneumococcal diseases.

L54 ANSWER 4 OF 22 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2002:607931 BIOSIS
DOCUMENT NUMBER: PREV200200607931
TITLE: Lactic acid bacteria for mucosal vaccines and therapy.
AUTHOR(S): **Hanniffy, S.** [Reprint author]; **Wells, J.** [Reprint author]
CORPORATE SOURCE: Institute of Food Research, Norwich, NR4 7UA, UK
SOURCE: Biochemical Society Transactions, (2002) Vol. 30, No. 5, pp. A110. print.
Meeting Info.: Biochemical Society 677th Meeting. Wales, Cardiff, UK. December 07-10, 2002.
CODEN: BCSTB5. ISSN: 0300-5127.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Nov 2002
Last Updated on STN: 27 Nov 2002

L54 ANSWER 5 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2001:338721 HCAPLUS
DOCUMENT NUMBER: 134:364015
TITLE: Sequences of antigenic **proteins** of a group B Streptococcus and the genes encoding them and their uses in vaccination
INVENTOR(S): **Le Page, Richard William Falla; Wells, Jeremy Mark; Hanniffy, Sean Bosco**
PATENT ASSIGNEE(S): Microbial Technics Limited, UK
SOURCE: PCT Int. Appl., 178 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001032882	A2	20010510	WO 2000-GB3437	20000907
WO 2001032882	A3	20011115		
W: CA, CN, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1214417	A2	20020619	EP 2000-958822	20000907
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 2003527100	T2	20030916	JP 2001-535564	20000907
US 2003170782	A1	20030911	US 2002-91007	20020306

PRIORITY APPLN. INFO.: GB 1999-21125 A 19990907
WO 2000-GB3437 W 20000907

AB The invention provides **protein** and DNA sequences of novel **protein** antigens from Streptococcus agalactiae, a group B Streptococcus. Their use in vaccines and screening methods is also described. Gene/partial gene sequences putatively encoding exported **proteins** in S. agalactiae have been identified using the nuclease screening system vis the LEEP (Lactococcus Expression of Exported **Proteins**) system. Genes containing signal sequences were identified using a nuclease reporter gene. Tru9I restriction digest fragments were cloned upstream of the nuclease gene and transformants screened using a DNA-Toluidine blue agar overlay which allowed colonies secreting the nuclease to be detected by formation of a pink halo. Mice vaccinated with a number of the genes showed statistically significant longer survival time than did unvaccinated controls when challenged with. S. agalactiae.

L54 ANSWER 6 OF 22 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:473135 BIOSIS
DOCUMENT NUMBER: PREV200100473135
TITLE: Heterologous gene expression in lactococcus, and the expression products therefrom.
AUTHOR(S): **Le Page, Richard William Falla** [Inventor, Reprint author]; **Wells, Jeremy Mark** [Inventor]; Wilson, Peter William [Inventor]; De Villareal, Pamela Norton [Inventor]
CORPORATE SOURCE: Cambridge, UK
ASSIGNEE: Microdial Technics Ltd., Cambridge, UK
PATENT INFORMATION: US 6221648 April 24, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Apr. 24, 2001) Vol. 1245, No. 4. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Oct 2001
Last Updated on STN: 23 Feb 2002

AB Heterologous **polypeptides** are produced in lactococcus using a T7 or T7-like RNA polymerase gene under the control of an inducible promoter effective in a lactococcus host, and a promoter specific for said polymerase upstream of a coding sequence for the heterologous **polypeptide**. Thus, the promoter specific for the polymerase directs transcription of the coding sequence selectively as a result of expression of the polymerase. The heterologous **polypeptide** can be produced at high yield,

and can be secreted. The **polypeptide** within the cell, being biologically active, can be delivered in the encapsulated form, e.g. as a medicament, vaccine or as an environmental pesticide.

L54 ANSWER 7 OF 22 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2002:201452 BIOSIS
DOCUMENT NUMBER: PREV200200201452
TITLE: Characterisation of a surface **protein** of Streptococcus pneumoniae that is protective against heterologous pneumococcal challenge.
AUTHOR(S): Hansbro, P. [Reprint author]; **Wells, J.**; **Le Page, R.**; Kyd, J.
CORPORATE SOURCE: Centre for Biomolecular Vaccine Technology, University of Newcastle, Newcastle, NSW, Australia
SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2001) Vol. 101, pp. 300. print.
Meeting Info.: 101st General Meeting of the American Society for Microbiology. Orlando, FL, USA. May 20-24, 2001. American Society for Microbiology.
ISSN: 1060-2011.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Mar 2002
Last Updated on STN: 20 Mar 2002

AB Streptococcus pneumoniae is a major global cause of morbidity and mortality resulting from such diseases as pneumonia, otitis media, septicaemia and meningitis. Some of these diseases result in more infection related deaths than all other vaccine preventable diseases combined. Adding to the problem is that antibiotic resistant strains are emerging at an alarming rate. Pneumococcal vaccines are available and utilise the capsular polysaccharide either alone or conjugated to immunogenic **proteins**. Polysaccharide vaccines do not elicit good immune responses in individuals most at risk and the pnuemococcus can change its' capsular type. Thus a **protein**-based vaccine is needed, however, all pneumococcal antigens discovered and tested so far are flawed when used as vaccines and novel surface **proteins** are needed.
Pneumococci have an unusual surface component, phosphorylcholine (PC), that binds to teichoic acids in the cell wall. Choline binding **proteins** (CBPs) bind to PC and are anchored to the cell surface. To date apprx12 CBPs have been discovered and characterised. We have isolated a set of these CBPs and used the mixture as a vaccine in both pneumococcal murine pneumonia and rat otitis media disease models. The mixture was shown to be protective against heterologous challenge in both models. Western blot of the anti-sera identified 2-3 **proteins** that dominated the response. One of these **proteins** was shown to provide similar protection against challenge when used alone as the immunising antigen. The different mechanisms of protection induced by this **protein** in the lung and middle ear are discussed along with the potential uses of this **protein** as a pneumococcal vaccine.

L54 ANSWER 8 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2000:98776 HCAPLUS
DOCUMENT NUMBER: 132:162025
TITLE: Novel Streptococcus pneumoniae **proteins** and nucleic acids and their uses as antigen/immunogen/vaccine, in detection/diagnosis, and screening anti-microbial targets
INVENTOR(S): **Le Page, Richard William Falla; Wells, Jeremy Mark; Hanniffy, Sean Bosco**; Hansbro, Philip Michael
PATENT ASSIGNEE(S): Microbial Technics Limited, UK
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000006738	A2	20000210	WO 1999-GB2452	19990727
W: CN, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1144640	A2	20011017	EP 1999-934990	19990727
EP 1144640	A3	20011128		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002521058	T2	20020716	JP 2000-562520	19990727
US 2003134407	A1	20030717	US 2001-769744	20010126

PRIORITY APPLN. INFO.:
GB 1998-16336 A 19980727
US 1999-125329P P 19990319
WO 1999-GB2452 W 19990727

AB Novel **proteins** from Streptococcus pneumoniae, nucleic acid sequences encoding them, antibody against them, and their uses in detection/diagnosis of Streptococcus pneumoniae infection are described. Their potential uses in vaccines and in screening methods are also described. A large number of genes putatively encoding exported **proteins** in S. pneumoniae were identified using the nuclease screening system. Some of the genes were successfully used as vaccines against Streptococcus pneumoniae infection in mice.

L54 ANSWER 9 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2000:98773 HCAPLUS
DOCUMENT NUMBER: 132:163385
TITLE: Antigenic **proteins** of a group B Streptococcus and the genes encoding them and their therapeutic uses
INVENTOR(S): **Le Page, Richard William Falla; Wells, Jeremy Mark; Hanniffy, Sean Bosco**
PATENT ASSIGNEE(S): Microbial Technics Limited, UK
SOURCE: PCT Int. Appl., 123 pp.

Searcher : Shears 571-272-2528

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000006736	A2	20000210	WO 1999-GB2444	19990727
WO 2000006736	A3	20000622		
W: CA, CN, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2337102	AA	20000210	CA 1999-2337102	19990727
EP 1100920	A2	20010523	EP 1999-934984	19990727
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2003138775	A1	20030724	US 2001-769736	20010126

PRIORITY APPLN. INFO.:
GB 1998-16335 A 19980727
US 1999-125163P P 19990319
WO 1999-GB2444 W 19990727

AB Novel **protein** antigens from Streptococcus agalactiae, a group B Streptococcus are described, together with nucleic acid sequences encoding them. Their use in vaccines and screening methods is also described. Genes containing signal sequences were identified using a nuclease reporter gene. TruI restriction digest fragments were cloned upstream of the nuclease gene and transformants screened using a DNA-Toluidine blue agar overlay which allowed colonies secreting the nuclease to be detected by formation of a pink halo. Mice vaccinated with a number of the genes showed statistically significant longer survival time than did unvaccinated controls when challenged with. S. agalactiae.

L54 ANSWER 10 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 1999:169939 HCAPLUS
DOCUMENT NUMBER: 131:2125
TITLE: 6-Phosphogluconate dehydrogenase from Lactococcus lactis: a role for arginine residues in binding substrate and coenzyme
AUTHOR(S): Tetaud, Emmanuel; Hanau, Stefania; **Wells, Jeremy M.; Le Page, Richard W. F.**; Adams, Margaret J.; Arkison, Scott; Barrett, Michael P.
CORPORATE SOURCE: Laboratoire de Biologie Moleculaire et Immunologie de Parasites Protozoaires, UPRESA-5016 CNRS, Universite Bordeaux II, Bordeaux, F-33076, Fr.
SOURCE: Biochemical Journal (1999), 338(1), 55-60
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A gene encoding 6-phosphogluconate dehydrogenase (6-PGDH, E.C. 1.1.1.44) was identified from the homofermentative lactic acid bacterium Lactococcus lactis, by complementation of Escherichia coli mutants. The cloned gene was then expressed to high levels in E.

coli and the **protein** purified for kinetic anal. The enzyme had a Km for 6-phosphogluconate of 15.4±1.4 μM and for NADP of 1.9±0.2 μM at pH 7.5. Sequence comparison of the L. lactis 6-PGDH with the corresponding enzyme derived from the pathogenic protozoan Trypanosoma brucei and sheep liver revealed the substrate-binding residues to be identical in all three species, although the three coenzyme-binding pockets differed slightly. A totally conserved arginine residue (Arg-447), believed to bind the 6-phosphate of substrate, was mutated to lysine, aspartate, alanine or tryptophan. In each case enzyme activity was lost, confirming an essential role for this residue on activity. A second arginine (Arg-34), believed to be critical in binding the 2'-phosphate of cofactor NADP+, was mutated to a tyrosine residue, as found in one atypical isoform of the enzyme in Bacillus subtilis. This alteration led to decrease in affinity for NADP+ of nearly three orders of magnitude. A second 6-PGDH gene has been identified from the genome of B. subtilis. This second isoform contains an arginine (Arg-34) in this position, suggesting that B. subtilis has two 6-PGDHs with different coenzyme specificities.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L54 ANSWER 11 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:509268 HCAPLUS
DOCUMENT NUMBER: 129:118773
TITLE: Cloning and expression of capsular polysaccharide genes in Lacotoccus lactis for vaccine production
INVENTOR(S): **Wells, Jeremy Mark; Le Page, Richard William Falla;** Gilbert, Christophe Francois Guy
PATENT ASSIGNEE(S): Microbial Technics Ltd., UK; Le Page, Richard William Falla
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9831786	A2	19980723	WO 1998-GB156	19980119
WO 9831786	A3	19981105		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9800387	A	19990716	ZA 1998-387	19980116
AU 9856719	A1	19980807	AU 1998-56719	19980119

EP 973864 A1 20000126 EP 1998-900912 19980119
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
JP 2001510342 T2 20010731 JP 1998-533958 19980119
PRIORITY APPLN. INFO.: GB 1997-939 A 19970117
WO 1998-GB156 W 19980119

AB Novel non-invasive or non-pathogenic gram-pos. microorganisms are provided which are transformed or transfected with DNA coding for one or more enzymes responsible for the production of a polysaccharide immunogen from a pathogenic bacterium. Vaccines comprising such microorganisms and their use in therapy are also provided, as are suitable DNA constructs and vectors. Thus, non-pathogenic, Gram-pos. Lactococcus lactis, Listeria monocytogenes, L. innocua, Staphylococcus xylosus, S. carnosus, Streptococcus gordoni, Lactobacillus and other microorganism were transformed with immunogenic capsular polysaccharide genes such as that encoding the capsule **protein** from Streptococcus pneumoniae. Other capsular **protein** genes can be obtained from Neisseria meningitidis, N. gonorrhea, Heaemophilus influenzae, Bacteroides fragilis, or other Gram-neg. pathogenic bacteria. The vaccine against a polysaccharide-encapsulated bacterium is adapted for nasal or oral administration.

L54 ANSWER 12 OF 22 MEDLINE on STN
ACCESSION NUMBER: 1998298037 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9632584
TITLE: Mucosal delivery of murine interleukin-2 (IL-2) and IL-6 by recombinant strains of Lactococcus lactis coexpressing antigen and cytokine.
AUTHOR: Steidler L; Robinson K; Chamberlain L; Schofield K M; Remaut E; **Le Page R W; Wells J M**
CORPORATE SOURCE: Department of Molecular Biology, Flanders Inter-University Institute for Biotechnology, and University of Ghent, B-9000 Ghent, Belgium.
SOURCE: Infection and immunity, (1998 Jul) 66 (7) 3183-9. Journal code: 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 19980716
Entered Medline: 19980709

AB Lactococcus lactis is a nonpathogenic and noncolonizing bacterium which is being developed as a vaccine delivery vehicle for immunization by mucosal routes. To determine whether lactococci can also deliver cytokines to the immune system, we have constructed novel constitutive expression strains of L. lactis which accumulate a test antigen, tetanus toxin fragment C (TTFC), within the cytoplasmic compartment and also secrete either murine interleukin-2 (IL-2) or IL-6. When mice were immunized intranasally with various different expression strains of L. lactis, the anti-TTFC antibody titers increased more rapidly and were substantially higher in mice immunized with the bacterial strains which secreted IL-2 or IL-6 in addition to their production of TTFC. This adjuvant effect was lost

when the recombinant strains of L. lactis were killed by pretreatment with mitomycin C and could therefore be attributed to the secretion of IL-2 or IL-6 by the recombinant lactococci. These results provide the first example of the use of a cytokine-secreting, noninvasive experimental bacterial vaccine vector to enhance immune responses to a coexpressed heterologous antigen and point the way to experiments which will test the possible therapeutic efficacy of this mode of cytokine delivery.

L54 ANSWER 13 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 1997:369765 HCAPLUS
DOCUMENT NUMBER: 126:339665
TITLE: Delivery of biologically active **polypeptides** by using transgenic non-pathogenic bacteria
INVENTOR(S): Steidler, Lothar; Remaut, Erik; **Wells, Jeremy Mark; Le, Page Richard William Falla**
PATENT ASSIGNEE(S): Cambridge University Technical Services Limited, UK; Steidler, Lothar; Remaut, Erik; Wells, Jeremy Mark; Le Page, Richard William Falla
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9714806	A2	19970424	WO 1996-GB2580	19961021
WO 9714806	A3	19970821		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG				
ZA 9608806	A	19980420	ZA 1996-8806	19961018
AU 9673154	A1	19970507	AU 1996-73154	19961021
EP 871748	A2	19981021	EP 1996-935054	19961021
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI				
CN 1202934	A	19981223	CN 1996-198487	19961021
BR 9610929	A	19991221	BR 1996-10929	19961021
NZ 320418	A	20000327	NZ 1996-320418	19961021
JP 2000508162	T2	20000704	JP 1997-515633	19961021
US 2001006642	A1	20010705	US 1998-60878	19980416
US 6605286	B2	20030812		
NO 9801746	A	19980622	NO 1998-1746	19980417
US 2003202991	A1	20031030	US 2003-350250	20030122

PRIORITY APPLN. INFO.:
GB 1995-21568 A 19951020
WO 1996-GB2580 W 19961021
US 1998-60878 A1 19980416

AB Disclosed are methods of delivering ≥1 biol. active

Searcher : Shears 571-272-2528

polypeptides and/or antigens by administering to a subject a non-pathogenic or non-invasive bacterium that expresses such **polypeptides** and/or antigens. The methods are clin. useful by, e.g., inducing the promotion of wound healing, inflammatory responses to injury and infection, or boosting immune response against tumor cells. Preparation of transgenic Lactococcus lactis that simultaneously expresses tetanus toxin fragment C (TTFC), mIL2, and mIL6 was demonstrated and used for immunization of mice. Transgenic Lactococcus lactis expressing interleukins and TTFC elicited in mice 10 times more anti-TTFC antibody than the L. lactis expressing TTFC alone. A pharmaceutical composition or a vaccine preparation containing such transgenic bacteria a drug delivery method is claimed.

L54 ANSWER 14 OF 22 MEDLINE on STN
ACCESSION NUMBER: 97362804 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9219268
TITLE: Oral vaccination of mice against tetanus with recombinant Lactococcus lactis.
AUTHOR: Robinson K; Chamberlain L M; Schofield K M; **Wells J M; Le Page R W**
CORPORATE SOURCE: Department of Pathology, University of Cambridge, UK.. kr204@mole.bio.cam.ac.uk
SOURCE: Nature biotechnology, (1997 Jul) 15 (7) 653-7. Journal code: 9604648. ISSN: 1087-0156.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970922
Last Updated on STN: 19970922
Entered Medline: 19970909

AB To determine whether a protective immune response could be elicited by oral delivery of a recombinant bacterial vaccine, tetanus toxin fragment C (TTFC) was expressed constitutively in Lactococcus lactis and administered orally to C57 BL/6 mice. The antibody titers elicited were lower than those following intranasal immunization (a route already known to result in high-level systemic anti-TTFC immune responses) but the protective efficacy was the same order of magnitude. The serum antibody isotypes elicited were predominantly IgG1 and IgG2a. TTFC-specific fecal IgA responses could be detected following oral or intranasal immunization. Chemically killed lactococci administered via the intranasal route were also able to elicit serum antibody responses of similar levels and kinetics to those induced by live bacteria.

L54 ANSWER 15 OF 22 EMBASE on STN
ACCESSION NUMBER: 96324572 EMBASE
DOCUMENT NUMBER: 1996324572
TITLE: Lactic acid bacteria as vaccine delivery vehicles.
AUTHOR: **Wells J.M.**; Robinson K.; Chamberlain L.M.; Schofield K.M.; **Le Page R.W.F.**
CORPORATE SOURCE: University of Cambridge, Department of Pathology,Cambridge CB2 1QP, United Kingdom

Searcher : Shears 571-272-2528

SOURCE: Antonie van Leeuwenhoek, International Journal of General and Molecular Microbiology, (1996) 70/2-4 (317-330).
ISSN: 0003-6072 CODEN: ALJMAO
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L54 ANSWER 16 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 1996:347759 HCAPLUS
DOCUMENT NUMBER: 125:55686
TITLE: Factors affecting the immunogenicity of tetanus toxin fragment C expressed in Lactococcus lactis
AUTHOR(S): Norton, Pamela M.; Brown, Henry W. G.; **Wells, Jeremy M.**; Macpherson, Angela M.; Wilson, Peter W.; **Le Page, Richard W. F.**
CORPORATE SOURCE: Department of Pathology, University of Cambridge, Tennis Court Road, Cambridge, CB2 1QP, UK
SOURCE: FEMS Immunology and Medical Microbiology (1996), 14(2-3), 167-177
CODEN: FIMIEV; ISSN: 0928-8244
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The relative immunogenicity of tetanus toxin fragment C (TTFC) has been determined in three different strains of inbred mice when expressed in Lactococcus lactis as a membrane-anchored **protein** (strain UCP1054), as an intracellular **protein** (strain UCP1050), or as a secreted **protein** which is partly retained within the cell wall (strain UCP1052). Protection against toxin challenge (20+LD50) could be obtained without the induction of anti-lactococcal antibodies. When compared in terms of the dose of expressed tetanus toxin fragment C required to elicit protection against lethal challenge the membrane-anchored form was significantly (10-20 fold) more immunogenic than the alternative forms of the **protein**.

L54 ANSWER 17 OF 22 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:90968 BIOSIS
DOCUMENT NUMBER: PREV199698663103
TITLE: Lon and Clp-like ATP-dependent proteases of Lactococcus lactis.
AUTHOR(S): Coward, C. [Reprint author]; **Lepage, R. W. F.** ; **Wells, J. M.**
CORPORATE SOURCE: Dep. Pathol., Univ. Cambridge, Tennis Court Rd., Cambridge CB2 1QP, UK
SOURCE: Ferretti, J. J. [Editor]; Klaenhammer, T. R. [Editor]; Brown, F. [Editor]; Gilmore, M. S. [Editor]. Dev. Biol. Stand., (1995) pp. 481-486. Developments in Biological Standardization; Genetics

Searcher : Shears 571-272-2528

of streptococci, enterococci and lactococci.
Publisher: S. Karger AG, P.O. Box, Allschwilerstrasse 10, CH-4009 Basel, Switzerland; S. Karger AG, New York, New York, USA. Series: Developments in Biological Standardization.
Meeting Info.: 4th International American Society for Microbiology Conference on Streptococcal Genetics. Santa Fe, New Mexico, USA. May 15-18, 1994.
CODEN: DVBSA3. ISSN: 0301-5149. ISBN: 3-8055-6207-1.

DOCUMENT TYPE: Book
Conference; (Meeting)
Book; (Book Chapter)
Conference; (Meeting Paper)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Mar 1996
Last Updated on STN: 4 Mar 1996

L54 ANSWER 18 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 1996:304902 HCAPLUS
DOCUMENT NUMBER: 125:29654
TITLE: Lon and Clp-like ATP-dependent proteases of Lactococcus lactis
AUTHOR(S): Coward, C.; **Le Page, R.W.F.**; **Wells, J.M.**
CORPORATE SOURCE: Department of Pathology, University of Cambridge, Cambridge, UK
SOURCE: Developments in Biological Standardization (1995), 85(Genetics of Streptococci, Enterococci and Lactococci), 481-486
CODEN: DVBSA3; ISSN: 0301-5149
PUBLISHER: Karger
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lactococcus lactis has been examined as possible bacterial delivery vector for systemic and mucosal immunization. It has been successfully used to express some **proteins** but only trace amts. of other **proteins** are formed. This apparent failure of the expression system could be due to proteolysis of expressed **proteins** by ATP-dependent proteinases such as Lon and Clp that recognize and degrade abnormal **proteins**. The presence of Lon and Clp-like proteinases in Lactococcus was examined The presence of gene clpL was detected in only two of eleven L. lactis strains tested, indicating that this gene is limited in its distribution or that it is poorly conserved. Restriction mapping suggests that at least three different genes may exist in the L. lactis clones isolated that complement Lon function.

L54 ANSWER 19 OF 22 MEDLINE on STN
ACCESSION NUMBER: 97077360 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8919927
TITLE: Progress in the development of Lactococcus lactis as a recombinant mucosal vaccine delivery system.
AUTHOR: Norton P M; **Le Page R W; Wells J M**
CORPORATE SOURCE: Department of Pathology, University of Cambridge, UK.
SOURCE: Folia microbiologica, (1995) 40 (3) 225-30. Ref: 10
Journal code: 0376757. ISSN: 0015-5632.

Searcher : Shears 571-272-2528

PUB. COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961231

AB The non-pathogenic, non-colonising Gram-positive organism Lactobacillus lactis is beeing developed as an antigen delivery system for mucosal vaccination. A high level expression system has been developed which allows loading of the bacterium with high levels of a heterologous antigen (TTFC) prior to inoculation. Mucosal inoculation of one such recombinant strain results in a protective serum antibody response and production of TTFC-specific IgA at mucosal sites.

L54 ANSWER 20 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 1993:619207 HCAPLUS
DOCUMENT NUMBER: 119:219207
TITLE: Regulated high-level expression of heterologous genes in Lactococcus using a bacteriophage RNA polymerase system
INVENTOR(S): **Le Page, Richard William Falla; Wells, Jeremy Mark;** Wilson, Peter William; De Villareal, Pamela Norton
PATENT ASSIGNEE(S): Lynxvale Ltd., UK
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9317117	A1	19930902	WO 1993-GB425	19930301
W: CA, GB, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
GB 2278358	A1	19941130	GB 1994-16471	19930301
GB 2278358	B2	19950726		
EP 628083	A1	19941214	EP 1993-904274	19930301
R: AT, BE, CH, DE, DK, ES, FR, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07504815	T2	19950601	JP 1993-514683	19930301
US 6221648	B1	20010424	US 1994-290995	19941027

PRIORITY APPLN. INFO.:
GB 1992-4237 A 19920227
GB 1992-19890 A 19920921
WO 1993-GB425 W 19930301

AB A method for achieving high level expression of heterologous genes in Lactococcus is described. The method places a T7 or T7-like RNA polymerase gene under control of an inducible promoter (e.g. derived from Lactococcus lactis) that is effective in the Lactococcus host

and the heterologous gene of interest under the control of a promoter responsive to the T7 polymerase. The promoter selectively directs the expression of the heterologous gene as a result of expression of the RNA polymerase gene. A Lactococcus signal sequence may be used to direct secretion of the final product. The bacteriophage RNA polymerase gene was placed under the control of a lactose-inducible promoter from Lactococcus and introduced into a lactose-utilizing L. lactis. Tetanus toxin gene fragment C was placed under control of a T7 polymerase promoter in a construct retaining the signal sequence of T7 gene 10 and introduced into the host carrying the RNA polymerase expression construct. Two hours after induction of transformants with lactose the TTFC gene product was the most abundant **protein** in the cells; when secretion expression vectors were use the **protein** accumulated in the medium. Levels of **protein** accumulation were not affected by vector copy number The **protein** produced a protective immune response in mice. The synthesis of HIV-1 V3 loop antigen and δ-endotoxins was also demonstrated.

L54 ANSWER 21 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 1994:27203 HCAPLUS
DOCUMENT NUMBER: 120:27203
TITLE: A model system for the investigation of heterologous **protein** secretion pathways in Lactococcus lactis
AUTHOR(S): **Wells, Jeremy M.**; Wilson, Peter W.; Norton, Pamela M.; **Le Page, Richard W. F.**
CORPORATE SOURCE: Dep. Pathol., Univ. Cambridge, Cambridge, CB2 1QP, UK
SOURCE: Applied and Environmental Microbiology (1993), 59(11), 3954-9
CODEN: AEMIDF; ISSN: 0099-2240
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The capacity of recombinant strains of Lactococcus lactis to secrete a heterologous **protein** was investigated by constructing two expression-secretion vectors (pLET2 and pLET3) for use with a lactococcal gene expression system driven by the highly active T7 RNA polymerase. The vectors incorporated different lactococcal secretion leaders and translation initiation sequences. When tetanus toxin fragment C (TTFC) was used as a test **protein** , the quantities of TTFC produced by the pLET2-TTFC strain exceeded the rate of secretion of TTFC into the growth medium. However, nearly all of the soluble TTFC associated with the cell (3.4%) was translocated through the cell membrane. The pLET3-TTFC strain did not accumulate TTFC intracellularly and exhibited growth characteristics and viability identical to the growth characteristics and viability of the control strain. This strain secreted approx. 2.9 mg of TTFC per L into the growth medium after 6 h of growth under test tube conditions. The results indicate that L. lactis is capable of secreting substantial amts. of heterologous **protein** and also confirm the findings of other workers that the cell wall may serve as a functional barrier to the diffusion of some secreted **proteins** into the growth medium.

L54 ANSWER 22 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 12
ACCESSION NUMBER: 1993:532530 HCAPLUS
DOCUMENT NUMBER: 119:132530
TITLE: Lactococcus lactis: high-level expression of tetanus toxin fragment C and protection against lethal challenge
AUTHOR(S): **Wells, Jeremy M.**; Wilson, Peter W.; Norton, Pamela M.; Gasson, Michael J.; **Le Page, Richard W. F.**
CORPORATE SOURCE: Dep. Pathol., Univ. Cambridge, Cambridge, CB2 1QP, UK
SOURCE: Molecular Microbiology (1993), 8(6), 1155-62
CODEN: MOMIEE; ISSN: 0950-382X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To determine if the food-grade bacterium L. lactis holds promise as a vaccine antigen delivery vector the authors investigated whether this bacterium can be made to produce high levels of a heterologous **protein** antigen. A regulated expression system has been developed which may be generally suitable for the expression of foreign antigens (and other **proteins**) in L. lactis. The system utilizes the fast-acting T7 RNA polymerase to transcribe target genes, and provides the first example of the successful use of this polymerase in a Gram-pos. bacterium. When the performance of the expression system was characterized using tetanus toxin fragment C (TTFC) up to 22% of soluble cell **protein** was routinely obtained as TTFC. Mice immunized s.c. with L. lactis expressing TTFC were protected from lethal challenge with tetanus toxin. L. lactis is able to express substantial quantities of a heterologous **protein** antigen and this organism can present this antigen to the immune system in an immunogenic form.

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